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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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			1645	

DATE MAILED: 04/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/039,760	<b>Applicant(s)</b> FINLAY ET AL.	
	<b>Examiner</b> Patricia A. Duffy	<b>Art Unit</b> 1645	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 12 October 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 33-90 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 33-90 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

The after final response filed 10-4-05 has been entered into the record.

The finality of the rejection of the last Office action is withdrawn in view of the new grounds of rejection set forth below.

Any objections and rejections not reiterated herein are withdrawn in favor of the new grounds of rejection set forth below.

#### *Priority*

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

#### *Drawings*

The drawings in this application have been approved.

#### *Specification*

The disclosure is objected to because of the following informalities:

The use of the trademarks Emulsigen Plus, VSA3 and Amphigen have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

#### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46, 48, 69, 60, 62, 79, 80, 81 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 46, 48, 60 and 62 the term "the cell protein" lacks antecedent basis in the claim. Further, the recitation renders the metes and bounds of the claim uninterpretable, because the composition comprises the cell supernatant and not the *E. coli* cell *per se*.

As to claim 69, the claim is *prima facie* indefinite because the term "the synthetic nonionic agent" lacks antecedent basis in claim 64.

As to claim 79, the claim is confusion because it specifically depends from a claim that states that the adjuvant is not oil-in-water using the term "non-oil-in-water" emulsion, but seeks to further limit to oil-based or water-in-oil based emulsions. As such, this claim is *prima facie* indefinite because it contradicts the claim from which it depends and the skilled artisan would not be able to ascertain the metes and bounds of a non-oil-in-water emulsion that is a water-in-oil based emulsion or oil-based emulsion.

As to claims 80, 81, and 82, the claims are *prima facie* indefinite from the use of the trademarks Emulsigen Plus<sup>TM</sup>, VSA3<sup>TM</sup> and Amphigen<sup>TM</sup>. Trademarks do not provide for a defined composition. As such, the skilled artisan would not be readily apprised of the metes and bounds of the emulsion. The (i.e.) after the trademark Emulsigen<sup>TM</sup> is not seen as limiting, because the composition that is represented by the trademark can change. Therefore, the trademarks as recited in the claims do not represent a defined chemical composition and as such their use in the claims renders the claims *prima facie* indefinite, unless specifically accompanied by the generic terminology.

*Claim Rejections - 35 USC § 102 and 103*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments

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Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33, 34, 37, 42, 51, 56, 63 and 73 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document).

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Kobayashi teaches a vaccine comprising supernatant from a vero cyst toxic strain of *E. coli* wherein the strain is culture by percolation and the upper supernatant liquid is centrifugally separated, percolated through a 0.45 um filter, formalin is added to obtain an supernatant immunogen. The vero cyst toxic immunogen is admixed with that obtained from cilia and the adjuvant aluminum gel is added preparing an inactivated vaccine. The vaccine is vaccinated subcutaneously or inside the muscle 2-3 times every other week (see pages 12-14 of the translation) to pregnant pigs. The specification acknowledges that at page 1, lines 17-20, that enterohaemorrhagic *E. coli* (EHEC) are also called Shiga toxin *E. coli* (STEC) and verotoxigenic *E. coli* (VTEC). The vero cyst toxic strain of Kobayashi is therefore necessarily enterohemorrhagic. Kobayashi teaches that a vaccine that is effective for all of the colon bacillus diarrhea would have to have enterotoxins (LT or ST), cilia and vero cyst toxicity (see page 9).

Claims 33, 34, 37, 38, 42, 51, 52, 56, 63 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) in view of Wilson et al (Journal of Food Protection, 60(11):1451-1453, 1997).

The teachings of Kobayashi are set forth above. Kobayashi et al differ by not teaching the vero cyto toxic *E. coli* serotype O157:H7.

Wilson et al teach that *E. coli* serotype O157:H7 is verocytotoxic and that controlling at the farm level may have a broader impact than simply reducing the risk of foodborne infection.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the verocytotoxic *E. coli* serotype O157:H7 of Wilson et al for the vero cyst toxic strain in method of making, composition and method of immunizing pigs of Kobayashi because Wilson et al teach that controlling at the farm

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level may have a broader impact on infection rates in man rather than simply reducing the risk of foodborne infection.

Claims 33, 34, 37, 38, 39, 42, 51, 52, 53, 56, 63 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) in view of Bochner (US Patent 6,136,554, issued October 24, 2000 and filed March 17, 1997).

The teachings of Kobayashi are set forth above. Kobayashi et al differ by not teaching the vero cyto toxic *E. coli* serotype O157:NM.

Bochner teach that *E. coli* serotypes producing verotoxin and are pathogenic including *E. coli* O157:NM and O157:H7 are verocytotoxic and enteroinvasive and all of the verotoxigenic strains produce potentially life-threatening disease (column 9, Table 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute any of the verocytotoxic *E. coli* serotypes O157:H7 or O157:NM of Bochner for the vero cyst toxic strain in method of making, composition and method of immunizing pigs of Kobayashi because Bochner teaches these are pathogenic strains that produce verocytotoxins that are potentially life-threatening.

Claims 33, 34, 37, 40, 51, 54, 63, 64, 74, 77, 78 and 83-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) in view of Harlow et al (Antibodies: A Laboratory Manual, Cold Spring Harbor Press, 1988, pages 96-99).

The teachings of Kobayashi are set forth above. Kobayashi et al differ by not teaching the different claimed adjuvants/emulsifiers.

Harlow et al teach that non-specific stimulators of the immune response are known as adjuvants. The judicious use of adjuvants is essential to induce a strong antibody response to soluble antigens. Most adjuvants comprise two components. One is a



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substance designed for form a deposit protecting the antigen from rapid catabolism. The two traditional methods of forming a deposit are to use mineral oils or aluminum hydroxide precipitates. With mineral oils, such as those used in Freund's adjuvant, the immunogen is prepared in a water-in-oil emulsion. Alternatives to the delivery systems include liposomes or synthetic surfactants such as pluronic polyols. The second component needed for an effective adjuvant is a substance that will stimulate the immune response nonspecifically. Compounds such as Lipid A, a derivative of toxic LPS is commonly used in liposome formulations. Harlow et al teach that the most commonly used adjuvant is Freund's adjuvant. Freund's adjuvant is a water-in-oil emulsion prepare with nonmetabilizable oils. When prepared with killed *M. tuberculosis* it is referred to as complete Freund's adjuvant, without the bacteria it is known as incomplete Freund's adjuvant. The killed *M. tuberculosis* bacteria component of complete Freund's adjuvant comprise muramyl dipeptide, cell wall extract, bacterial DNA, and a bacterial complex. Freund's is one of the best adjuvants for stimulating strong and prolonged responses (page 98). Harlow et al teach that the most active component of *M. tuberculosis* is localized to muramyl dipeptide (see page 96). Harlow et al teach that antigens, preferably in saline are mixed with an equal volume of the adjuvant oil and an emulsion is formed (page 98).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the adjuvant formulations of Harlow et al for the aluminum gel of Kobayashi because Harlow teaches that complete Freund's adjuvant is one of the best adjuvants for stimulating strong and prolonged responses.

Claims 33, 34, 37, 42, 51, 56, 63, 64 and 65, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) in view of Morein et al (Methods: A Companion to Methods in Enzymology, 19(1):94-102, 1999).

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The teachings of Kobayashi are set forth above. Kobayashi et al differ by not teaching the different claimed adjuvants/emulsifiers.

Morein et al teach that ISCOMS have the ability to immunomodulate an immune response. The ISCOM is a stable complex consisting of cholesterol, phospholipids, adjuvant-active saponins and antigen. ISCOMS prominently enhance antigen targeting, uptake and activity of antigen presenting cells. ISCOMS have been shown to be an efficient delivery system for the newborn and mucosal administration (see abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the ISCOM adjuvant formulations of Morein et al for the aluminum gel of Kobayashi because Morein et al teach that ISCOMS have the ability to modulate an immune response and are an efficient delivery system for newborns and for mucosal administration.

Claims 33, 34, 37, 40, 51, 54, 56, 63, 64, 65, 69, 71, 74, 76, 77, 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) in view of Allison (Methods: A Companion to Methods in Enzymology, 19:87-93, 1999).

The teachings of Kobayashi are set forth above. Kobayashi et al differ by not teaching the different claimed adjuvants/emulsifiers.

Allison teaches that squalene is a linear hydrocarbon found in many tissues, notably the livers of sharks and other fishes. Allison teaches that squalene and its fully hydrogenated derivative squalane are metabolized. Allison teaches that microfluidized squalene or squalane emulsions are efficient adjuvants. The emulsions are stable for years at ambient temperature and can be frozen. Antigens are added after emulsification so that conformational epitopes are not lost by denaturation and to facilitate manufacture. Additionally, plurionic block copolymer can be added and other immunomodulators can be added, such as a relatively non-toxic analog of muramyl dipeptide (see page 87, abstract).

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Allison teaches Hjorth Adjuvant formulation 1 comprising and emulsion of 10% squalene, 1% lecithin and 0.2% Tween 80 (page 91, column 2) and Hjorth Adjuvant Formulation 2 comprising and emulsion of 5% squalene, 20% glycerol, and 0.2% Tween 80. Allison teaches that squalene emulsions appear to be the least toxic formulations and may be useful with a wide variety of antigens. Allison teaches that squalene and squalane emulsions can be used to develop routinely administered human and veterinary vaccines.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the adjuvant formulations of Allison for the aluminum gel of Kobayashi because Allison et al teach that squalene emulsions appear to be less toxic and may be useful with a wide variety of antigens. It would have been further obvious to the ordinary artisan to include a plurionic block copolymer and/or muramyl dipeptide analog in the vaccine adjuvant formulation as combined directly above because Allison teaches that these agents can boost the immune response.

Claims 33, 34, 37, 40, 42, 43, 44, 51, 54, 56, 57, 58, 63, 64, 65, 69, 71, 72, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) in view of Pokric, Periodicum Biologorum 101(4):823-302, 1999).

The teachings of Kobayashi are set forth above. Kobayashi et al differ by not teaching the different claimed adjuvants/emulsifiers.

Pokric teaches adjuvant emulsions including oil-in water, water-in-oil and water in-oil-in-water, suitable for formulation with an adjuvant for antigen vaccine formulation. Pokric teaches that formulation of antigen with adjuvant emulsions provide for a more effective immunization (page 283, Introduction and page 285 column 2, first full paragraph). Pokric teaches Freund Complete Adjuvant FCA), that contains mineral oil, surfactant mannide monooleate (Arlacel A) and heat killed *M. tuberculosis* cells. It is used

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as a W/O emulsion prepared by admixing equivalent volumes of FCA and water antigen solution so that the water/oil ratio is usually 1:1. Pokric teaches Freund Incomplete Adjuvant (FIA) which is the same as FCA lacking the *M. tuberculosis* components. Pokric teach that the limited adjuvant activity of FIA is corrected by administering with other adjuvant compounds such as saponins, cytokines and muramyl dipeptide (page 272-293). Pokric teach TiterMax which is also a water-in-oil emulsion comprising microparticulate silica, squalene and synthetic bloc copolymer CRL-8941 as both the emulsifier and the immunomodulator (i.e. adjuvant) component (page 293). Pokric teaches syntax adjuvant formulation-1 (SAF-1) that is comprised of a mixture of aqueous solution of tMDP and W/O emulsion of squalene or squalene stabilized by Pluornic L-121 (10%) POE and Tween 80 (page 293, column 2). Pokric teach that W/O emulsions have immunostimulating properties of the same level of PCA, FIA and TiterMax formulations in stimulating an antibody response but without the adverse side-effects. Such formulations prepared with metabolizable fatty acid esters and non-toxic Plunoric L-121 as an emulsifying agent. Other W/O emulsions are butyl sterate/ethyl caprate (1:9) wherein the butyl stearate is the adjuvant and the caprate provides for low viscosity. Pokric teaches oil-in-water emulsions have the advantage that they are less viscous and easier to inject as compared to W/O emulsions. Pokric teach an O/W emulsion of t-MDP, containing Pluronic L121 block copolymer, Tween 80 and squalene that generates both an antibody and cell mediated immunity (page 294, second full paragraph). Pokric teach that MF59 is a O/W emulsion consisting of stable droplets of the metabolizable oil squalene (5% v/v) and two surfactants the water-based Tween 80 (0.5% v/v) and oil-phase Arlacel 80 (0.5% v/v). MF59 has been demonstrated to be a potent stimulator of both humoral and cell-mediated immunity. Pokric et al teach Lipovant. Lipovant is a oil-adjuvant based on lecithin, glycerine and peanut oil. Pokric teach Ribi's Adjuvant system (RAS) that is a combination of commercially available squalene (2% v/v), TDM and different immunostimulators (page 295). Pokric teaches water-in-oil-in-water emulsions in which single W/O emulsions were

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re-emulsified in the non-ionic detergent Tween 80. Pokric teaches that a light W/O/W emulsion is characterized by a high 2/1 water/oil ratio. It is composed of 33% v/v light mineral oil Bayol, 3.3% v/v aqueous-phase surfactant Tween 80, 3% v/v oil-phase surfactant Arlacel 83. The ration of water phase/oil phase surfactants amounts to 1:1. Finally, Pokric teach montanide emulsions ISA (Incomplete Seppic Adjuvant) adjuvants are a group of oil-surfactant based adjuvants which different surfactants are combined with either a non-metabolizable mineral oil, a metabolizable oil or a mixture of them.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute any of the adjuvant emulsion formulations of Pokric for the aluminum gel of Kobayashi because Pokric teaches that antigens in a adjuvant emulsion render immunization more effective.

Claims 33, 34, 37, 40, 41, 42, 43, 44, 51, 54, 55, 56, 57, 58, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 74, 75, 76, 77, 78, 79, 80, 81, 82, 86, 87 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) in view of Littell-van den Hurk et al (US Patent 5,951,988 issued September 14, 1999, filed June 5, 1995).

The teachings of Kobayashi are set forth above. Kobayashi et al differ by not teaching the different claimed adjuvants/emulsifiers.

Littel-van den Hurk et al teach adjuvant formulations containing quaternary ammonium salts in conjunction with an oil which maybe a mineral oil, an animal oil or a vegetable oil or mixture thereof, or an oil-in-water emulsion of one or more such oils are useful for incorporation with antigen as nonspecific immunostimulatory formulations (i.e. the instant adjuvant; see abstract). Littell-van den Hurk et al teach preparation of a DDA/Oil Adjuvant formulation. Vaccines were prepared by mixing antigen with DDA (dimethyl....bromide - claim 87), Tween 80 and EMULSIGEN PLUS™ (see column 6, Example 1) or mixing the antigen with EMULSIGEN PLUS™ or avridine

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(NN...propanediamine; claim 88). Littel-van den Hurk et al teach VSA3 in a adjuvant formulation. Littel-van den Hurk et al teach animal oils such as cod, halibut, shark and vegetable oils such as almond, sesame, soybean and the like (column 4, lines 49-55). Littel-van den Hurk et al teach adjuvant formulations comprising quaternary ammonium salts and solvent therefore, an emulsifier, and a biological buffer. The emulsifiers include sodium and ammonium salts of oleic and lauric acids, organic sulfonates such as sodium lauryl sulfate, cationic agents such as cetyltrimethylammonium bromide, nonionic agents are glyceryl glycol esters and ethers such as sorbitan monopolmitate and acacia, gelatin, lecithin and cholesterol (paragraph bridging columns 4-5). The preferred amounts of the components of the adjuvant formulation are found at column 5, lines 20-34). Littel-van den Hurk et al teach that the adjuvants can be used in any vertebrate subject including cattle and pigs.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute any of the adjuvant emulsion formulations of Littel-van den Hurk et al for the aluminum gel of Kobayashi because Littel-van den Hurk et al teaches that antigens in a adjuvant emulsion enhance the immune response toward the antigen(s).

Claims 47, 48, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) and Pokric (Periodicum Biologorum 101(4):823-302, 1999) as applied to claims 33, 34, 37, 40, 42, 43, 44, 51, 54, 56, 57, 58, 63, 64, 65, 69, 71, 72, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84 and 85 above, and further in view of Finlay (WO 99/24576, published May 20, 1999).

The teachings of Kobayashi and Pokric as combined are set forth supra.

Finlay et al teach a bovine vaccine against enterohemorrhagic *E. coli* by making a vaccine with the combination of intimin, Tir, EspA, EspB or a combination thereof. Finlay

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et al teaches that bovine/cattle/cows so vaccinated block adherence of *E. coli* in vaccinated cows and therefore vaccinated cattle do not become *E. coli* carriers (i.e. continually shed in feces; see page 51, example XI).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention to add to the vaccine of Kobayashi and Pokric as combined *supra* the isolated vaccine proteins of Finlay et al and immunize a porcine or bovine animal for protection against infection and carrier state because Finlay et al teach that vaccination of cattle with these enterohaemorrhagic proteins can protect against infection (attachment) and the carrier state (shedding into feces). It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to combine the members of the subunit vaccine as combined *supra* in equal ratios to provide for easy combination and one would have been motivated to combine the individual components in a concentration or percent to optimize the vaccine response and the

Claims 33, 34, 35, 36, 37, 40, 45, 46, 49, 50, 51, 54, 56, 59, 60, 63, 64, 65, 69, 71, 74, 76, 77, 78, 79 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) in view of Findlay (WO 99/24576, published May 20, 1999).

The teachings of Kobayashi are set forth above. Kobayashi et al differ by not combining the vaccine with intimin, Tir, EspA, EspB or combinations thereof or vaccinating cattle/cows/bovine.

Finlay et al teach a bovine vaccine against enterohemorrhagic *E. coli* by making a vaccine with the combination of intimin, Tir, EspA, EspB or a combination thereof. Finlay et al teaches that bovine/cattle/cows so vaccinated block adherence of *E. coli* in vaccinated cows and therefore vaccinated cattle do not become *E. coli* carriers (i.e. continually shed in feces; see page 51, example XI).

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It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention to add to the vaccine of Kobayashi et al, the isolated vaccine proteins of Finlay et al and immunize a porcine or bovine animal because Finlay et al teach that vaccination of cattle can protect against infection (attachment) and the carrier state (shedding into feces). It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to combine the members of the subunit vaccine as combined supra in equal ratios to provide for easy combination and one would have been motivated to combine the individual components in a concentration or percent to optimize the vaccine response.

Claim 90 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) and of Finlay (WO 99/24576, published May 20, 1999 as applied to claims 33, 34, 35, 36, 37, 40, 45, 46, 49, 50, 51, 54, 56, 59, 60, 63, 64, 65, 69, 71, 74, 76, 77, 78, 79 and 89 above, and further in view of Kudva, (Diss. Abstr. Int., B 1998, 58(10):5252).

The combination of Kobayashi (JP 59020226, published Feb 1, 1984; translation attached to original Japanese document) and of Finlay (WO 99/24576, published May 20, 1999 is set forth above. The combination differs by not immunizing sheep with the combination.

I would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to administer the composition of Kobayashi and Finlay as combined supra to the sheep of Kudva because Kudva teaches that enterohemorrhagic E. coli also colonize sheep and sheep are a reservoir for this important pathogen.

#### *Citation of Relevant Art*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.



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Hunt et al, J. Clin. Pathol., 42:847-852, 1989 is cited to teach that enterohaemorrhagic *E. coli* are those that are very cytotoxin producing and teach that as early as 1983 that vero cytotoxin-producing *E. coli* (VETC) (mostly serotype 0157:H7) were associated with haemorrhagic colitis.

### *Status of the Claims*

All claims stand rejected.

### *Conclusion*

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 7:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Primary Examiner

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